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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,251	07/12/2001	Jiangping Wu	9555.94USI1	3075

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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
ROBINSON, HOPE A

ART UNIT	PAPER NUMBER
1653	6

DATE MAILED: 06/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,251	WU ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Abstract

1. The abstract is objected to because the following words are misspelled "against" appears as "aganst" (see line 4) and "immuno-suppressive" appears as "immuno-suppressinve" (see line 9).

Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-12 are rejected under 35 U.S.C. 112 first paragraph, because the specification, while being enabling for a method of inhibiting T and B cell proliferation with lactacystin (see page 13+) and only for treating cells with lactacystin, does not reasonably provide enablement for a method of reversing the ongoing activity of any activated blood cells, comprising administering an effective amount of a proteasome inhibitor to an individual in need of such treatment (see claim 1) nor for the claimed "analogs thereof" (see claim 10). *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) lists the factors to be considered when determining whether there

is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include but are not limited to: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the predictability of the art; and (g) the breadth of the claims.

Quantity of Experimentation:

The specification is absent data or examples of a method of reversing the ongoing action of activated blood cells with the administration of a proteasome inhibitor to an individual. Furthermore, there is no demonstration of a method employing analogs thereof for lactacystin. In addition, neither the claims nor the specification provides a clear definition as to what ongoing activity of activated blood cells is being reversed by the claimed method. Further, it is unclear as to what the desired effect is once the treatment is administered. Thus, one of skill in the art would have to engage in undue experimentation to be able to practice the claimed invention commensurate in scope with the claims.

Amount of Direction/Guidance:

The specification is absent data with a showing of treatment for an individual suffering from septic shock, adverse immune response or inflammation. Claim 4 recites the co-administration of an immunosuppressive drug, yet the disclosure does not provide any dosage information or data on the use or the effect of the drug. In view of the foregoing, the specification is not enabled because it does not provide adequate guidance to be able to practice the claimed invention.

Presence or Absence of Working Examples:

The specification is absent exemplification of the claimed analogs thereof and to examine all the possible "analogs thereof" would require undue experimentation. Therefore, at the time the application was filed, would not have taught one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

Nature of the invention/State of the prior art/Predictability of the art/Breath of the claims:

The nature of the claimed invention is a method of reversing an ongoing proliferation or activity, or both, of activated blood cells, comprising administering an effective amount of a proteasome inhibitor to an individual in need for such a treatment. The claim broadly reads "activity" and there is no indication of what activity or if all activity of an activated blood cells is reversed. The method aims at administering a proteasome inhibitor and there is no indicia as to how much, what disease or ailment is being treated or what end result is desired. The level of skill in the art does not compensate for the inadequate guidance provided in the instant specification, thus, the claimed invention is unpredictable.

Thus, for the reasons stated above the claimed invention lacks enablement for the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph as failing to distinctly point out the subject matter applicant regards as his invention.

Claim 1 is rejected as being indefinite because the claim recites " a method for reversing the ongoing activity of activated blood cells" without defining what activity is being reversed. Further the claim is indefinite for reciting "administering an effective amount of a proteasome" since the quantity is undefined as to what it must do. It is also unclear as to what the end point of this treatment is suppose to be. Additionally, it is not clear what condition the individual is being treated for or what disease. The dependent claims are included in this rejection.

Claims 7-9 lack antecedent basis because the specification disclose that administration of LAC results in apoptosis (cell death) of activated blood cells, thus the cells in independent claim 1 are already dead, however these claims seem to be indicating that the activated blood cells are undergoing inhibition of energy and oxygen supply etc. which implies that they are not yet dead.

Claim 10 is indefinite as to whether the "or analogs thereof" refer to the lactacystein or to dipeptide boronic acid or to" proteasome inhibitor".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1, 4 and 6-11 are rejected under 35 U.S.C. 102 (a) as being anticipated by Wang et al. (The Journal of Immunology, vol. 160, no. 2, pages 788-801, January 15, 1998).

Wang et al. teach a method for reversing proliferation of activated blood cells (T and B cells), comprising administering an effective amount of a proteasome inhibitor to an individual in need of such a treatment (claim 1, see Abstract, Figure 1 and page 792). Wang et al. teach peripheral blood T cells stimulated with PHA (claim 4) and the inhibition of T and B cell proliferation with LAC (see claims 10 and 11, Figure 1 of the reference). Wang et al. also teach that as a result of blockage of cycling, the activated, but not the resting, T cells underwent apoptosis when treated with LAC (claim 6, page 790). As apoptosis is the death of a cell, claims 7-9 are anticipated because the cell taught by the reference would have experienced inhibition of energy, oxygen supply and a disruption of mitochondrial function and nitric acid synthesis. Thus, the limitations of the claims are met by this reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

6. Claims 1-12 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Wang et al. (The Journal of Immunology, vol. 160, no. 2, pages 788-801, January 15, 1998) in view of Schreiber et al. (WO 96/32105, October 17, 1996), Armistead et al. (U.S. Patent No. 5,665,774, March 8, 1993) and Adams et al. (U.S. Patent No. 5,780,454, July 14, 1998).

Wang et al. teach a method for reversing proliferation of activated blood cells (T and B cells), comprising administering an effective amount of a proteasome inhibitor to an individual in need of such a treatment (claim 1, see Abstract, Figure 1 and page 792). Wang et al. teach peripheral blood T cells stimulated with PHA (claim 4) and the inhibition of T and B cell proliferation with LAC (see claims 10 and 11, Figure 1 of the reference). Wang et al. also teach that as a result of blockage of cycling, the activated, but not the resting, T cells underwent apoptosis when treated with LAC (claim 6, page 790). Wang et al. teach that LAC induces apoptosis (cell death) therefore, it would be expected that the dying cell would experience inhibition of oxygen and energy (claim 7), disruption of mitochondrial function (claim 8) and disruption of nitric acid synthesis (claim 9). Wang et al. do not expressly teach treatment of individuals with adverse

immune response/inflammation/septic shock. However, Schreiber et al. teach LAC in a method to treat inflammation (claim 2, page 85). Schreiber et al. teach that chronic or acute inflammation can result from transplatation rejection (i.e. tissue grafts, skin grafts, organ of any type etc.) or autoimmune diseases (claim 3, page 87). In addition, Schreiber et al. teach a treatment which includes reversing, reducing or arresting the symptoms, clinical signs and underlying pathology of a condition in a manner to improve or stabilize the subject's condition (claim 1, page 81). Neither Wang et al. or Schreiber et al. teach the immunosuppressants recited in claim 5, however, Armistead disclose a method of administering the immunosuppressants FK-506, cyclosporin A and rapamycin to control or reverse chronic rejection of allografts in a transplantation patient (claim 5, column 9).

In-so-far-as Wang et al., Schreiber et al. and Armistead et al. do not teach the proteasome inhibitor DPBA, Adams et al. teach that boronic acid and ester compounds are potent and highly selective proteasome inhibitors (claim 12, column 3).

In view of the foregoing, one of ordinary skill in the art would have had the claimed invention as a whole based on the teachings of the above references. One of ordinary skill would have been motivated to combine the teachings of the references because Wang et al. teach a method to reverse proliferation in activated blood cells (T and B cells) by administering LAC, a known proteasome inhibitor. In addition, one of skill in the art would have been motivated to replace the inhibitor taught by Wang et al. with that of Adams et al., with a reasonable expectation of success because boronic acid compounds are potent inhibitors of the proteasome. Moreover, the claimed invention is obvious because Armistead et al. teach the use of immunosuppressants to control or reverse allografts. Therefore, the combined teachings of the references result in a process for reversing proliferation or activity in activated peripheral blood T and B

cells (Wang et al.) by administering a proteasome inhibitor (Wang et al./Schrieber et al./Adams et al.) to a patient suffering from adverse immune response/inflammation (Schreiber et al.) and the co-administration of immunosuppressive drugs (Armistead et al.) which are known to control and reverse chronic rejection from allografts. Thus, the claimed invention was obvious to make and use at the time it was made was *prima facie* obvious.

Conclusion

7. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope Robinson whose telephone number is (703) 308-6231. The examiner can normally be reached on Monday-Friday from 9:00 am to 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S. F. Low, can be reached at (703) 308-2923.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-4242. Please affix the examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Hope Robinson, MS

Patent Examiner

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600